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Fibromyxoid Sarcoma in a Four-Year-Old Child: Case Report and Review of the Literature

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We present a child with a rare and chemotherapy-resistant form of soft-tissue cancer, low-grade fibromyxoid sarcoma, first noted when he was 4 years old. He is the youngest patient reported to date.

An 11-year-old white male presented to The University of Texas M. D. Anderson Cancer Center's Department of Pediatrics with a 7-year history of right thigh mass and pulmonary nodules, confirmed on examination. He had undergone extensive prior chemotherapy and surgery. He received chemotherapy with high-dose cyclophosphamide (7 g/m^2) and later etoposide (150 mg/m^2/day × 5), with only slight shrinkage of the thigh mass and none in the lungs. Subsequently the tumor in his proximal thigh and his lung metastases were resected, and radiation therapy was administered to the thigh. His disease remained stable for 12 months, but he then developed a pleural-based metastasis on the left side and new, bilateral lung metastases also. The tumors on the left side were removed; residual disease is stable after treatment for 6 months with subcutaneous alpha-interferon-2b.

Low-grade fibromyxoid sarcoma is very uncommon in children. It grows slowly and metastasizes to distant organs, chiefly to the lungs. It is resistant to conventional chemotherapy, and thus far only surgery seems to have a life-prolonging effect. Newer chemotherapeutic and possibly biologic agents should be tried in future patients, in order to find an effective way to control the disease.

Key words: fibromyxoid sarcoma, childhood, interferon-alpha

INTRODUCTION

Low-grade fibromyxoid sarcoma is a distinctive soft-tissue neoplasm with a tendency to occur in young adults. It is an indolent sarcoma with a deceptively benign histologic appearance that can nevertheless metastasize to distant organs, most commonly to the lungs. It has no particular site of predilection and can arise from any region where other soft-tissue sarcomas occur. Histologically, it is characterized by bland cytologic features, contrasting fibrous and myxoid areas and a swirling, whorled growth pattern. Although it is not an extremely rare tumor, it is very uncommon in children. Here we report the youngest patient to date.

CASE REPORT

The patient was first noted to have a mass measuring 3 × 3 cm in his right distal thigh in 1986, when he was 4 years old. The mass was removed and the initial diagnosis was uncertain; possibilities included hemangiopericytoma or fibrosarcoma. Six months later another mass measuring 1 × 1 cm was resected from the same region and was histologically diagnosed as fibrosarcoma. In 1989, when he was 6.5 years old, nodules were demonstrated bilaterally on chest radiographs, along with a new mass in the right proximal thigh, which was removed. He then received chemotherapy consisting of vincristine (1.5 mg/m^2 IV weekly times 12 doses), intravenous doxorubicin (total dose of 120 mg/m^2), and cyclophosphamide (40 mg/kg IV times 4 doses). No change was noted in the metastatic disease in his lungs. In 1993, when he was 10 years old, a chest radiograph revealed that his lung nodules were bigger, although no new nodules were evident. He was then treated with vincristine (1.5 mg/m^2 IV times 9 doses), intravenous doxorubicin (total dose of 160 mg/m^2), ifosfamide (7 gm/m^2 IV times 4 doses), and cisplatin (90 mg/m^2 IV times 4 doses), with no apparent response of the metastases to the chemotherapy.

He first presented to the Department of Pediatrics at The University of Texas M. D. Anderson Cancer Center for evaluation of his persistent disease in August, 1993, when he was 11 years old. The only pathologic finding on physical examination was a 10 × 10 cm mass in his right proximal thigh. His chest films showed extensive

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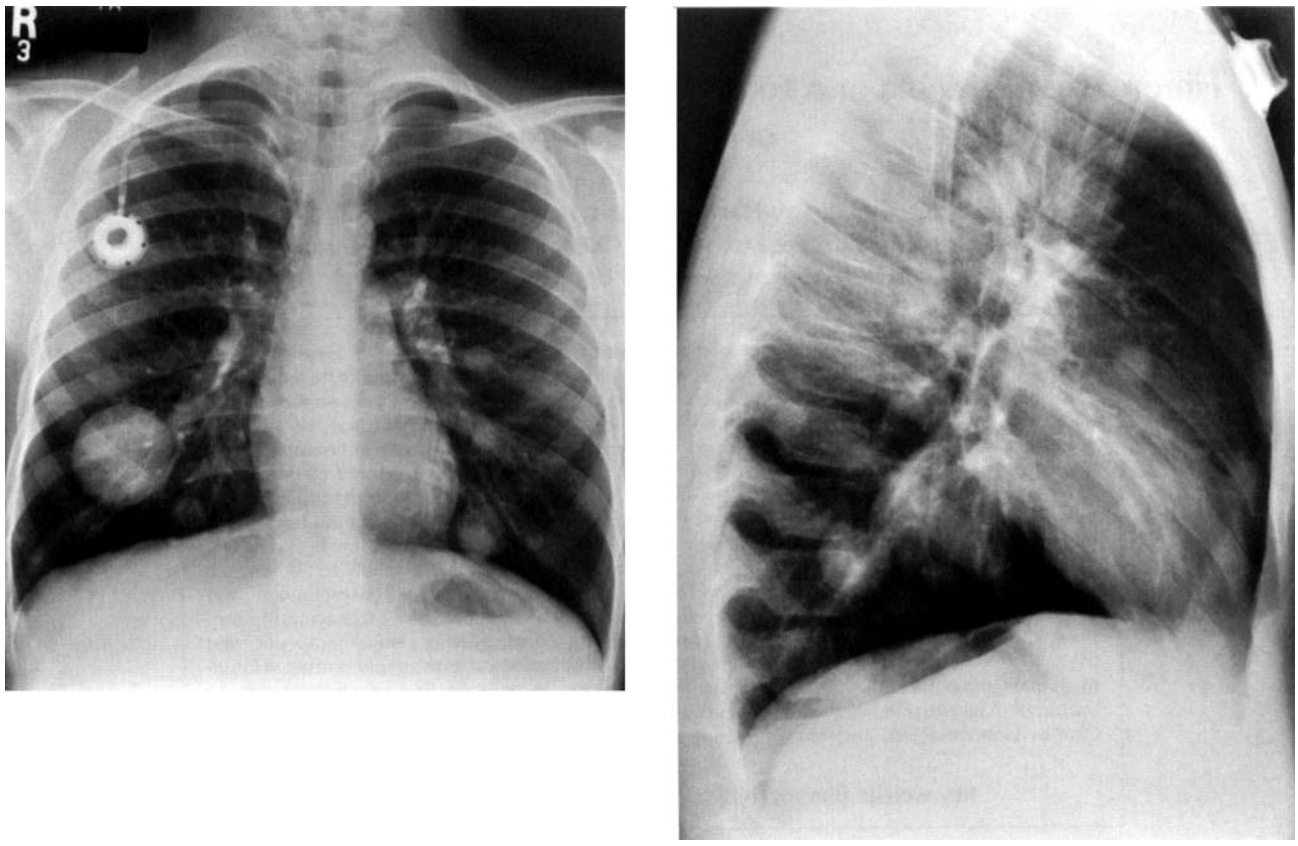

Fig. 1. Posteroanterior and lateral radiographs of the chest display multiple bilateral lung metastases at the time of referral in August, 1993.

and scattered lung metastases (Fig. 1). Review of the outside slides of the 1989 groin mass (HLE) revealed a diagnosis of low-grade fibromyxoid sarcoma. Because the tumor was resistant to standard chemotherapy regimens, a decision was made to try high-dose (7 g/m^2) intravenous cyclophosphamide [1]. Three weeks later, the thigh tumor had decreased in size by 25%, but the lung metastases were unchanged. A trial with etoposide (150 mg/m^2 IV for 5 days) failed to produce any further response in the thigh or lungs.

The chemotherapy-resistant character and slow evolution of his tumors led us to consider surgical treatment. The right thigh tumor was resected and multiple wedge resections of pulmonary metastases were accomplished. The pathologic specimens again revealed low-grade fibromyxoid sarcoma. Because margins of the resected material from the thigh were not tumor-free, it was decided to administer radiation therapy to that region for microscopic residual disease. He received 60 Gy of radiation in 30 fractionated doses over 6 weeks, using 6 MeV photons and 15 MeV electrons. Six weeks after the resolution of postoperative changes, a follow-up chest film showed a single pulmonary nodule in his left upper lobe that had gone unnoticed during the initial operation. The patient later underwent a left thoracotomy for the resection of this single metastatic nodule. He was then followed with physical examination and chest radiographs every 3 months, and was well with no progression of his disease until age 12, 14 months after his initial visit to our clinic. At that time, a follow-up chest-computed tomographic scan showed a large pleural-based mass in the left posterior chest, along with several suspicious smaller nodules in the lung parenchyma bilaterally. The pleural mass was removed.

Because conventional chemotherapeutic agents had had little, if any, effect on his disease, we considered trying a biologic agent. Alpha-interferon-2b, like interferons in general, has little efficacy against advanced soft-tissue sarcoma [4–6]. However, one adult patient with recurrent intra-abdominal low-grade fibromyxoid sarcoma was given alpha-interferon-2b on an experimental protocol at The University of Texas M. D. Anderson Cancer Center, at 10 million units per square meter subcutaneously three times per week for 4 months beginning in June, 1990. The tumor was stable 2 months later and was slightly smaller 2 months after that. The interferon was continued on the same schedule for 4 years, during which time the tumor remained stable. Therapy was then

stopped. Serial scans showed no change 2 months later, but the tumor appeared slightly larger 4 months after the interferon was discontinued. Reinstitution of the interferon is being considered [7].

Accordingly, we began giving our patient alpha-interferon-2b at 12.5 million units subcutaneously three times a week (10×10^6 U/m^2). He has tolerated this treatment with mild fever and chills, ameliorated by acetaminophen orally. The residual small lung nodules have not changed over a 6-month period, and no new lesions have appeared on serial-computed tomographic scans.

DISCUSSION

Low-grade fibromyxoid sarcoma was first described by Evans in 1987 as an indolent but metastasizing soft-tissue neoplasm with a deceptively benign histologic appearance [2]. He reported two women in their late 20s, whose tumors were located in the soft tissues of the scapular region and the axillary-chest wall area, respectively. Both patients were treated with surgery alone. Lung metastases later developed in one of them; in the other, lung nodules were present at the time of diagnosis. The first patient died 94 months after excision of the primary neoplasm, whereas the second was alive 82 months after surgery. Six years later, 12 cases of patients aged 6 to 51 years at diagnosis (including the original two) were reported by the same author [3]. The tumor was located in the thigh or inguinal area in four patients, in the shoulder area in three patients, and in the axilla-chest wall area, the perineum, the small bowel mesentery, the neck, and the buttock in one patient each. Median tumor size was 9.5 cm. On follow-up, nine of the 12 patients (75%) had experienced local tumor recurrence. Distant metastasis occurred in seven patients (58%), mainly to the lungs. At latest follow-up, four patients had died of tumor at 8, 9, 31, and 31.5 years, respectively; three were alive with recurrent or metastatic disease, and five were alive and tumor-free many years after diagnosis.

Low-grade fibromyxoid sarcoma has also been described in several other publications. In the first, Devaney et al. [8] reported a case in a 17-year-old girl who developed multiple lung metastases 8 years after removal of a 1 cm, vimentin-positive nodule in the neck; she was well 18 months later, after receiving unspecified systemic chemotherapy [8]. Nichols and Cooper [9] reported a case in the arm of a 52-year-old man. Immunostaining showed a positive vimentin and negative desmin stain. The CD-34 stain was positive, which helped to exclude aggressive fibromatosis, nodular fasciitis, and fibrosarcoma [9].

Recently Goodlad et al. [10] have summarized 11 cases in patients aged 11 to 65 years old at diagnosis, of whom 10 were male. Two were recently detected, but six of the other nine with follow-up of 1.5 to 15 years had developed one or more local recurrences, and one also had pulmonary metastases with local recurrence 4 years after initial diagnosis. These authors review the criteria by which low-grade fibromyxoid sarcoma is distinguished from similar entities. In brief, the low-grade fibromyxoid sarcoma contains spindle and stellate cells with uniform nuclei, and often a few small nucleoli, arranged in a whorled pattern with alternating areas of fibrous and myxoid stroma; the cells routinely contain vimentin and only rarely smooth muscle actin or other tissue-specific substances. Other disorders which need to be distinguished by histology and/or immunostaining techniques include neurofibroma (evidence of neural differentiation, S-100 protein positive), fibromatosis (fascicular architecture, not whorled; plump, vesicular nuclei; actin-positive), dermatofibrosarcoma protuberans (dermal or subdermal location, storiform pattern, CD34-positive), malignant peripheral nerve sheath tumor (elongated, wavy nuclei; partially fascicular, and S-100-positive), myxofibrosarcoma (lacks fibrous stroma and whorled tumor cells), and spindle cell liposarcoma (has atypical adipocytes). Their report provides strong support for the existence of low-grade fibromyxoid sarcoma as a separate diagnostic entity [10].

Our case represents the youngest patient ever reported in the literature. Low-grade fibromyxoid sarcoma is very uncommon in the childhood age group. Among the 25 cases already reported, four were in children 6, 14, 17, and 18 years old at the time of diagnosis. Our patient was 4 years old when his tumor was initially detected. In spite of aggressive surgical and chemotherapeutic treatment, his disease has recurred multiple times both locally and distantly, and he currently has another recurrence 10 years after the initial diagnosis.

Low-grade fibromyxoid sarcoma is a tumor that shows slow but often relentless evolution. Among Evans' cases, the longest living patient, who had both local recurrence and lung metastases at last follow-up, was alive 50 years after initial diagnosis. In his series of 12 patients, six received chemotherapy and two chemotherapy plus radiation therapy, in addition to surgical procedures on the primary and metastatic tumors. In all of them, disease had failed to respond to therapy or had recurred despite variable amounts of drugs and radiation. Because low-grade fibromyxoid sarcoma is a very slowly growing tumor, its resistance to chemotherapy is not surprising. The main treatment modality that might have an impact on the final outcome of this disease seems to be surgery. The role of radiation therapy in achieving local control is unknown. One of Goodlad's patients received 5,040 cGy of external-beam radiatherapy in 28 treatment sessions after his second local recurrence, but he had another local recurrence one year later [10]. Our patient was treated with chemotherapeutic agents that are known to be active against soft-tissue sarcomas but still had recrudescence of lung metastases in the absence of local recurrence, despite

prior complete resection of his lung nodules. The stabilization of his disease after treatment with alpha-interferon-2b is encouraging, but hardly conclusive. He may need this agent for an extended period of time [11].

These cases show that metastases are not necessarily preceded by local recurrence and that completeness of excision does not necessarily prevent the development of later metastases. Therefore, it is appropriate to recommend that new chemotherapeutic or biologic agents be tried, one at a time, in patients with measurable disease, in order to discern whether there is any drug or biologic material that will favorably affect the course of this disease.

ADDENDUM

Nine months after institution of alpha-interferon-2b, a left pleural-based lesion noted previously was enlarging, and two other small, new lesions were noted in the left lung on CT scan. Alpha-interferon-2b was increased to 1×10^6 units/m^2 5 days per week. Two months later, the pleural lesion had grown slightly, as had another left pulmonary lesion. Interferon was increased to daily administration; six weeks later, a new right-sided lesion was noted. Bilateral staged thoracotomies were performed 14 months after alpha-interferon-2b had been initiated. The nodules were very similar microscopically to the previous specimens, and there was no evidence of an inflammatory response or lymphocytic infiltrate. Interferon was discontinued and oral etoposide is now being given (50 mg/m^2/day for 21 consecutive days followed by a 7-day rest).

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